ImmunoTools IT-Box-Cy55M-Award 2013

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The effect of fibroblast hyaluronan on innate immunity in the lung

A common feature of a number of respiratory distress models such as allergic airway disease, non-infectious bleomycin lung injury and bacterial infections such as *Klebsiella* and *Streptococcal* pneumonias is an accumulation of hyaluronic acid (HA) in the airway. HA generated during lung injury is a damage-associated molecular pattern (DAMP), detected through TLR-2 and TLR-4. Triggering of TLRs on macrophages by HA results in the expression of early inflammatory cytokines such as MIP-1α, MIP-1β, MCP-1, IL-8 and RANTES which develop and maintain an immune response. Interestingly, TLR signalling by HA results in a novel NF-κB/I-κBα regulatory loop; resulting first in activation of NF-κB and then its auto-inhibition. Additionally, HA induces the TLR negative regulators A20 and IRAK-M; an effect that is dependent on the binding of HA to its major cell surface receptor, CD44.

Hyaluronan is synthesised by HAS1, 2 and 3, which are expressed on stromal cells such as airway smooth muscle, fibroblasts and both endothelium and epithelium; and my PhD project involves characterisation and manipulation of the expression of these genes in various respiratory infection models. To explore the inflammatory stimuli required to induce HAS expression, recombinant mouse cytokines such as TNF-a, IL-1b, IFN-g as well as growth factors such as FGF-1 and -2 would be used to recreate the cytokine environment found during disease in order to determine the contribution of specific subsets of stromal cells to the synthesis of HA. Access to a broad range of mouse recombinant cytokines would allow us to profile the effect that a Th1, Th2 or Th17 response has on the expression of HA synthases.

We would also use cytokines such as MIP-1, MCP-1 and RANTES to recreate the exact cytokine milieu induced by stimulation of cells by HA, in order to further characterise the contribution of HA to disease pathology.

ImmunoTools *IT-Box-Cy55M* for **Thomas Bell**
includes 55 recombinant mouse cytokines

rm EGF, rm Eotaxin / CCL11, rm FGF-a / FGF-1, rm FGF-b / FGF-2, rm FGF-8, rm Flt3L / CD135, rm G-CSF, rm GM-CSF, rm GRO-a / CXCL1, rm GRO-b / CXCL2, rm IFNgamma, rm IL-1alpha, rm IL-1beta, rm IL-2, rmIL-3, rm IL-4, rm IL-5, rm IL-6, rm IL-7, rm IL-9, rm IL-10, rm IL-11, rm IL-13, rm IL-15, rm IL-16, rm IL-17A, rm IL-17C, rm IL-17F, rm IL-19, rm IL-20, rm IL-21, rm IL-22, rm IL-25 / IL-17E, rm IL-27, rm IL-31, rm IL-33, rm IP-10 / CXCL10, rm LIF, rm MCP1 / CCL2, rm M-CSF, rm MIP-1α/ CCL3, rm MIP-1β / CCL4, rm MIP3α / CCL20, rm MIP3β / CCL19, rm NGF-beta, rm PDGF-AA, rm PDGF-BB, rm RANTES / CCL5, rm sCD40L / CD154, rm SCF, rm SDF-1α / CXCL12a, rm SDF-1β / CXCL12b, rm TNFα, rm TPO, rm VEGF DETAILS.